



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,202	01/22/2004	Guping Tang	4249-0115P	2330
2292 7590 10/26/2007 BIRCH STEWART KOLASCH & BIRCH PO BOX 747 FALLS CHURCH, VA 22040-0747			EXAMINER MAKAR, KIMBERLY A	
			ART UNIT	PAPER NUMBER
			1636	
			NOTIFICATION DATE	DELIVERY MODE
			10/26/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

**Advisory Action
Before the Filing of an Appeal Brief**

Application No.

10/761,202

Applicant(s)

TANG ET AL.

Examiner

Kimberly A. Makar, Ph.D.

Art Unit

1636

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05 October 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
(a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☒ They raise the issue of new matter (see NOTE below);
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: See Continuation Sheet. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
The status of the claim(s) is (or will be) as follows:
Claim(s) allowed: _____.
Claim(s) objected to: _____.
Claim(s) rejected: 1, 2, 5-19 and 21-29.
Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____.
13. ☐ Other: _____.

/Daniel M Sullivan/
Primary Examiner
Art Unit 1636

Continuation of 3. NOTE: The claims, as amended, include the new limitation "wherein the cyclodextrin is modified at no more than two position by an activating agent to allow attachment to no more than two polyethylenimine molecules" which is a limitation that had not been searched previously. This amendment thus would require additional searches of the art. Additionally, this phrase introduces new matter into the claims which is not supported by the specification, as there is no support for this phrase in the specification.

Continuation of 11. does NOT place the application in condition for allowance because: Applicants traverse, and present arguments against the 112 written description and the 103 rejection of the final office action.

Applicant's arguments are persuasive over the written description in part. The specification does not provide support for "to no more than two polyethylenimine molecules." The specification does have support for "modified at no more than two positions" as evidenced by figure 1. Thus the 112 rejection is maintained.

Applicants also traverse the 103(a) rejection of claims 1-2, 5-9, 11-12, 16-18, 21-25 and 29 as being obvious over Kosak (US Patent Publication 2001/0034333) in view of David (US Patent 6,509,323). Applicants argue that the claims cannot encompass a CyD-CyD or PEI-PEI bond due to the use of CDI as a linker moiety. Applicant point out that copolymer of PEI and CyD taught by Kosak is not a linear polymer and, and that the PEI-CyD copolymer are not within the "backbone" of the polymer as in the present invention, but are pendant side chains, and that the examiner was merely picking and choosing from the teachings of Kosak to result in the present claims. Applicants also argue that the Examiner failed to address the limitation of Cyd only has two activated sites. Applicant point to the teachings of Davis as the PEG simply serves to link the CyD and does not play a role in the delivery of therapeutic compound and "the presence of ester groups and a polyethylene structure is only incidental" and is also based on impermissible hindsight. Applicant goes on to state that the PEI is not among the monomer units taught by Davis.

The examiner is not persuaded by applicant's arguments:

In response to applicant's arguments that the claims cannot encompass as CyD-CyD or PEI-PEI due to the use of CDI as a linker moiety, the examiner disagrees. With the exception of claims 10 and 19, the instant claims are not limited to the use of CDI as a linker moiety, therefore applicant's argument that CyD-CyD or PEI-PEI is not possible does not apply to the remaining claims.

Furthermore, Applicants argue that cyclodextrin comprises only hydroxyl groups, however according to the specification as filed, modified cyclodextrin is also encompassed by the term "cyclodextrin." See paragraph 0021 of the instant specification:

[0021] Preferably, the cyclodextrin is a modified cyclodextrin. More preferably, the cyclodextrin is .beta.-cyclodextrin modified or activated to allow attachment to polyethylenimine. In a preferred form, the .beta.-cyclodextrin is activated by .beta.-1,1'-carbonyldiimidazole. Although .beta.-1,1'-carbonyldiimidazole has been found to be suitable to activate cyclodextrin, other agents suitable for this purpose include but are not limited to benzotriazole carbonate, N,N'-disuccinimidyl carbonate, chloroformates, N-hydroxysuccinimidyl chloroformate, and carbonylimidazole.

While applicant is correct in that Examiner stated that Kosak does not expressly teaches that copolymer is linear, a rereading and analysis of Kosak reveals that the Kosak inherently teaches a linear polyethylenimine. The term "polyethylenimine" would have the name "polymethylene(methyl)imine" if it was branched: which means that the polymer would be: -N-CH₂(CH₃)-N- where the methyl is branched from the methylene: thus only one carbon between nitrogens. So inherently, Kosak thus does teach a linear polyethylenimine.

In response to applicant's arguments that the examiner used improper hindsight and "picking and choosing" when reading from Kosak and Davis, the Examiner disagrees. It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Secondly, the examiner was not picking and choosing from the teaching of Kosak, but was constructing embodiments from the teaching of Kosak from a finite selection of polymers, which Kosak teaches are all parts of the polymer compounds of his invention. The MPEP 2105 teaches that it would be obvious to exchange similar structures of especially when the art teaches the exchange of similar compounds:

(c) Consider the Teachings of Structural Similarity

Consider any teachings of a "typical," "preferred," or "optimum" species or subgenus within the disclosed genus. If such a species or subgenus is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties. See, e.g., *Dillon*, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also *Deuel*, 51 F.3d at 1558, 34 USPQ2d at 1214 ("Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."). The utility of such properties will normally provide some motivation to make the claimed species or subgenus. Id.

Additionally, the examiner disclosed the following teaching from Kosak, reiterated herein:

Kosak teaches that the cyclodextrins are coupled in a process known as "capping":

Capping is a type of derivatizing defined herein as coupling any suitable chemical "capping substance" to two or more sites on the CD molecule so that the substance spans the area between the coupled sites. Preferably, the capping substance spans across one of the end openings of the CD molecule and thereby stops the passage of a guest molecule through the capped CD molecule. Paragraph 0206

The CD's used herein can be suitably complexed with one or more guest molecules and/or derivatized and/or capped before, during or after their incorporation into the water-soluble CD polymer carrier of the instant invention. In addition, the derivatizing and/or capping can be a done to produce CD's with the desired substances coupled to specific locations on the CD molecule. (paragraph 0206 and 0208) Preferably, the capping substance is coupled at the primary or secondary "end" of the CD molecule, forming a bridge across either (or both) opening(s) that includes suitable hydrophobic groups in the capping substance. The capping substances can be coupled directly to available hydroxyls on the CD, or they can be coupled to suitable functional groups such as; diamino (or triamino), compounds to iodinated CD, or azido compounds to sulfonlated hydroxyls, and/or through "spacers" added to the CD. Paragraph 0210.

Alternatively, other amino compounds have been coupled to the oxidized CD such as hydrazine, adipic add dihydrazide, glutamic acid, beta-phenylethylamine, laurylamine and cystamine. Many other useful amino compounds can be coupled to the oxidized CD or CD-block such as polypeptides, 6-amino-N-hexanoic acid, arginine, protamines, N-(2-aminoethyl)-1,3-propanediamine (AEPD), polyethylenimine (PEI) and nucleic acids. Paragraph 0284 of Kosak.

Thus Kosak teaches that the derivatization occur and that "two or more" site on the CD molecule, which occurs directly to the hydroxyls on the CD. Thus, Kosak teaches "two OR more" in the alternative, so one embodiments includes "no more than two" modification on the cyclodextrin. The limitation of "wherein each cyclodextrin moiety is attached to one or two polyethylenimine moieties and not to any other cyclodextrin moiety" is newly added, and has not been addressed before.

In response to applicants argument that Davis's polymers inherently express "the present of ester groups and a polyethylene structure is only incidental" and that "the argument is structurally similar to PEI so it offers teaching pertinent to the present invention is simply based on impermissible hindsight" the examiner disagrees. Applicants thus also recognize that the PEI and PEG are structurally similar. The fact that PEI itself is not reactive with CyD is not a persuasive argument, since the claims are not directed toward a method of making the polymer, but to a composition comprising all of the limitations of the polymer. Applicant also admits that Davis does teach a linear copolymer of CyD and PEG.

Applicant argues that PEI is not among the "monomer A" structures of Davis. The examiner agrees. David made monomer units of Cyclodextrin modified at no more than two positions (see claim 9) and a polylinker of PEG. The examiner never stated that Davis taught the polylinker was PEI. Davis suggested that the polylinker would be a "polyethylene polymer" (column 17, lines 10-15), and that Kosak taught polyethylene and Cyclodextrin polymers.

In conclusion, the claims are not limited to any particular linear order of the copolymer, therefore to the extent that the claims recite a copolymer comprising...PEI and cyclodextrin, the scope of the claims would encompass, PEI-PEI-CyD-CyD. Applicants have provided no evidence of non-obviousness, the prior art cited clearly suggests making copolymers of PEI and CyD, including wherein PEI is linear. Thus the 112 and 103(a) rejections are proper and is maintained..